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(73) Proprietor: **COLUMBIA LABORATORIES, INC.**
16400 NW 2nd Avenue
Miami Florida 33169 (US)

(72) Inventor: **Robinson, Joseph R.**
41 Chequamegon Bay, Madison
53719 Wisconsin (US)

(74) Representative: **Fisher, Adrian John et al**
CARPMAELS & RANSFORD
43 Bloomsbury Square
London WC1A 2RA (GB)

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Descripti n

Technical Field

The present invention contemplates a method for moisturizing of skin and mucous membranes, and particularly contemplates a method of moisturizing that includes the use of a particular bioadhesive.

Background Art

Several conditions produce drying or desiccation of membranous tissue of the body. These conditions produce dry mouth (xerostomia), dry eye (sicca conditions), dry vaginal, dry nasal or dry rectal mucosa, and/or dry skin that are aesthetically unpleasing and/or irritating to the individuals manifesting such conditions.

Methods for moisturization of dry tissue principally utilize creams, lotions, gel or salves that are applied to the affected tissue in an attempt to prevent further dehydration of the tissue by placing a water-impermeable hydrophobic barrier over the treated tissue. Petrolatum, mineral oil, lanolin and isopropyl myristate are exemplary hydrophobic materials so used. These preparations are of limited usefulness over a prolonged period of time.

Hydrophilic small molecules such as glycerin and glycerin/water mixtures, urea, and propylene glycol are known humectants said to be useful in moisturizing skin. Naturally occurring macromolecules such as collagen, hyaluronic acid, elastin and placental proteins have also been used as humectants. Another naturally occurring macromolecule proteolipid obtained from epidermal tissues of several mammals is reported in European Patent Application 86118139.4 (publication No. 0\228\711 A 2, published July 15, 1987), and said to possess humectant properties making it useful in a moisturizer for human skin.

Several synthetic hydrophilic materials, which in the presence of water adhere to the skin and/or mucous membranes, have been used by themselves or in conjunction with one or more active agents to treat various pathological conditions, but not dryness of the skin or mucosa. These hydrophilic materials are often referred to in the art as hydrogels.

Exemplary of such materials are the complex of sulfated sucrose and aluminum hydroxide known generically as sucralfate and available under the trademark CARAFATE® from Marion Laboratories, Inc. of Kansas City, Missouri. Sucralfate is used alone or in conjunction with an antacid to treat duodenal ulcers. Another synthetic adherent material, designed for use in the buccal cavity, is a combination of gelatin, pectin and sodium carboxymethylcellulose in a plasticized hydrocarbon gel available under the trademark ORABASE® from Hoyt Laboratories Division of Colgate-Palmolive Co. of Needham, Massachusetts.

A mucosal adherent ointment based upon partly neutralized polymethacrylic acid methyl ester was recently reported by Bremecher et al., Arzneim.-Forsch./Drug Res., 33, 591 (1983). That ointment was reported to show a pseudoplastic quality without any thixotropic effect, good mucosal adhesion and no local irritation.

Numerous compositions are known that contain a medicinal component and a polymer carrier. These are generally known as delayed release compositions.

For example, in U.S. Patent No. 3,074,852, the hydrogel polymer carrier is disclosed as being a polymer of U.S. Patent No. 2,798,053, prepared by polymerization of polyalkenyl polyether as cross-linking agent with acrylic acid, or its equivalent. The polymerization is reported to be carried out in a hydrocarbon diluent with a free radical catalyst. The cross-linked polymer utilized contains acrylic acid cross-linked with about 0.75 to about 2 percent by weight of the polymer of a copolymerized polyalkenyl polyether. Exemplary polyalkenyl polyethers are disclosed as polyallyl sucrose or polyallyl pentaerythritol that are said to desirably contain an average of at least 3 allyl groups per molecule, the allyl groups being bonded by ether linkages. The exemplary cross-linked polymer is said to be CARBOPOL® 934. The polymer of particular interest in U.S. Patent 3,074,852 is said to be in acid form, and is more particularly described in U.S. Patent No. 2,909,462, which patent further describes its polymers as being agglomerated by steam action. That particularly described polymer is again reported to be the material sold as CARBOPOL® 934 by B.F. Goodrich Chemical Company.

A neutral hydrogel of a polymer of ethylene glycol methacrylate or similar monomer cross-linked sufficiently to make the polymer insoluble is disclosed in U.S. Patent No. 3,551,556. Exampl 8 of that patent also discloses an acid-containing hydrogel prepared by the copolymerization of methacrylic acid and maleic anhydride to form what appears to be a linear, noncross-linked polymer.

U.S. Patent No. 3,641,237 discloses hydrogels films prepared by polym rization of lower alkoxy lower alkyl acrylates and methacrylates along with a 0-40 percent of a hydrophilic acrylic monomer in the

presence of a cross-linking agent. Various monomers are disclosed as useful for the 0-40 percent co-monomers, including hydroxyalkyl acrylates and methacrylates, salts of alpha,beta-unsaturated organic acids and strong acid salts of polymerizable ethylenically unsaturated amine-containing monomers.

European Patent Office Publication No. A1 0 043 319 discloses hydrogel copolymers that contain about 30 to 80 percent acrylate or methacrylate alkyl monoester, about 5 to 68 percent acrylic or methacrylic acid and about 2 to about 15 percent of a bi- or tri-functional acrylate or methacrylate ester. Exemplary bi-functional ester cross-linking agents are ethylene and polyethylene glycol diacrylates. Trimethylolpropane triacrylate and triethylolpropane trimethacrylate are exemplary tri-functional esters.

U.S. Patent No. 4,226,848 discloses a composition for adhering a pharmaceutical preparation to the mucosa of the oral or nasal cavities. The composition disclosed contains a water-swellable and mucosa-adherent polymeric matrix comprising (a) about 50 to about 95 percent by weight of a cellulose ether and (b) about 50 to about 5 percent by weight of a homo- or copolymer of acrylic acid or a pharmaceutically acceptable salt thereof, with a pharmaceutically effective amount of a medicament dispersed therein.

It is stated in that patent that when either material of the adherent composition is used singly in producing a pharmaceutical preparation, the resulting preparation is unsuitable as a slow-releasing preparation because it does not adhere to the mucosa of the oral or nasal cavity or even when it adheres, it is relatively rapidly disintegrated, dispersed or dissolved by the saliva or other secretions. The specified ratio of the two polymers that form the polymeric matrix is reported to be essentially required in order for the slow-releasing preparation disclosed in that patent not to cause whitening of the mucosa and to release the medicament at a controlled rate. It is further reported that when the polyacrylic acid or salt portion of that composition is present at greater than about 50 percent by weight, the preparation irritates the mucosa, and causes whitening of the mucosa and the marked occurrence of blisters thereon.

The polyacrylic acid or salt portion of the preparation of U.S. Patent No. 4,226,848 is also described as being water-soluble or water-swellable, but is further described as having a desired, specific range of viscosities at a concentration of 0.2 percent by weight in water. Thus, if that polymer is not truly soluble in water, it is dispersible to at least a sufficient extent to obtain the desired viscosity. An exemplary acrylic acid polymer disclosed therein is the lightly cross-linked acrylic acid-allyl sucrose copolymer available under the trademark CARBOPOL® 934 from B.F. Goodrich Chemical Co., which is said to form a high viscosity gel-like dispersion in water.

U.S. Patent No. 3,158,538 related to antidiarrheal compositions and their methods of use. The patent discloses use of a composition containing a resin possessing selective intestinal-swellability in conjunction with a tertiary amine anticholinergic agent. The useful resins are said to generally be irregular weight carboxylic type ion-exchange resins loosely cross-linked by means of about 0.2-2.0 weight percent by weight of a polyunsaturated copolymerizable cross-linking agent but which have only a negligible amount of uncross-linked chains present.

One group of polymers said to be useful in No. 3,158,538 are the polycarboxylic acids cross-linked by a polyalkenyl polyether as are disclosed in U.S. Patent No. 2,798,053. Those are the CARBOPOL® 934-type polymers noted previously.

Another disclosed group of allegedly useful polymers is said to be those disclosed in U.S. Patent No. 2,810,716. The polymers of that patent are polycarboxylic acids cross-linked by 0.01-2 weight percent of a cross-linker such as a dihydroxydiene or divinyl benzene. The polymers of U.S. Patent No. 2,810,716 are also described in U.S. Patent No. 3,202,577 as being useful for diarrhea treatments.

Still another group of polymers disclosed as useful along with the amine-containing cholinergic in U.S. Patent No. 3,158,538 are the materials described in U.S. Patent No. 2,923,692. Those polymers are said to be swellable, water-insoluble materials useful as mucilages. They are prepared from a carboxylic acid-containing ethylenic monomer and a cross-linking agent such as divinyl benzene, a diene polymer or polyalkenyl polyethers of polyols. The cross-linker is present at 0.1 to 10.0 percent in those mucilages. The polymers are prepared in a hydrocarbon solvent for the monomers that is a non-solvent for the polymer. After polymerization, the polymer is at least partially neutralized and ground to a size of 100-325 mesh.

Still further, U.S. Patent No. 3,158,538 teaches that the resin as usually administered consists of hard, sand-like, gritty granules of resin approximately 12 to 14 mesh. The sizes of such mesh are 1.70 millimeters (mm) and 1.40 mm, respectively, according to the Table of Standard Test Sieves (Wire Cloth) found at page F-143 of the Handbook of Chemistry and Physics, 54th ed., CRF Press, Cleveland, Ohio (1973).

U.S. Patent No. 3,390,050 teaches the preparation and use of polycarboxylic acid/medicament-containing beads. Each of th examples that illustrate that invention utiliz s a solution of preformed copolymer to which are admixed the medicam nt and an acrylate or methacrylate monomer or mixture of monomers. The monomer-medicament-copolymer admixture is thereafter emulsifi d and polymerized to form beads. That patent furth r teaches that the monomers used are made into a physiologically acceptable

polymer of adequate strength that can be at least swollen, e.g., dissolved by the gastric juices.

U.S. Patent No. 3,121,043 discloses sustained release preparations based upon the interaction of a cross-linked carboxylic acid or anhydride-containing polymer and an amine-containing drug. U.S. Patent No. 4,192,827 teaches a water-insoluble hydrophilic gel that is used as a carrier for medicaments. The material is pr pared from about 30-90 percent of a hydrophilic polymer or copolymer and about 10-70 percent cross-linker that is a terminal diolefinic hydrophobic macromer having a molecular weight of about 400 to about 8000. U.S. Patent No. 4,450,150 teaches a biodegradable, implantable drug depot and methods of making and using it. The biodegradable polymer portion of the depot is a glutamic acid/ethyl glutamate copolyamide that contains about 5 to about 50 mole percent glutamic acid.

U.S. Patent No. 4,548,990 discloses a controlled-release drug delivery composition whose cross-linked polymeric portion is prepared from monomers that include 50-99 percent of a water-insoluble monoolefinic monomer or mixture. The polymer is said to swell in ethanol and in water with a swelling ratio of 2:1 to 22:1.

The following teachings relate to body insert structures that are suitable for controlled-release of a medicament.

U.S. Patents No. 3,811,444 and No. 4,014,987 describe inserts, and specifically ocular inserts. Both require the use of hydrophobic polycarboxylic acids that contain one ionizable carboxylic acid group per 8-22 carbon atoms.

U.S. Patent No. 4,271,143 teaches an aqueous dispersion of an ophthalmic drug and a high molecular weight polymer. The disclosed polymers are water-soluble or dispersible to an extent that the viscosity of an aqueous composition can be measured. The two polymers mentioned as useful are CARBOPOL® and an ethylene-maleic acid copolymer.

U.S. Patent No. 4,478,818 teaches an intraocular depot device that provides controlled-release of a steroid, such as fluorometholone, in two different forms. In one embodiment, the polymers said to be useful for encapsulating the depot device are said to be substantially impermeable to the passage of the steroid solute, but are permeable to the passage of biological fluid and water. Imbibed fluid is said to generate osmotic pressure that ruptures the polymer and permits release of the steroid.

In a second embodiment, the paired steroids are housed in a so-called diffusional insert having a size of 1-15 mm by 0.1-7.5 mm. These inserts are said to be fabricated from a wide range of non-specific polymers said to be insoluble in ocular fluids.

U.S. Patent No. 4,553,973 discloses a drug-containing walled osmotic device that contains a compartment having a passageway communicating with the exterior of the device. The wall is comprised of a cellulose ether and a permeability enhancer. The semipermeable wall can also contain a water-soluble acrylic acid polymer or a water-insoluble acrylic acid polymer such as CARBOPOL®.

U.S. Patent No. 4,608,048 discloses a multi-compartmented osmotic device for drug delivery. Some embodiments of the disclosed invention include a hydrophilic film-forming material permeable to the passage of external fluid but impermeable to passage of drug. That film is said to be makable from polyacrylic or methacrylic acids or mixtures thereof cross-linked with divinyl benzene.

Still further, U.S. Patent No. 4,615,697 of the present inventor, inter alia, discloses the use of a polymer that is commercially referred to as polycarbophil as a bioadhesive in the dispensing of a therapeutic agent in controlled release compositions. Another patent of the present inventor, U.S. Patent No. 4,795,436, discloses the use of such a polymer sized to pass through a 100 mesh sieve screen with fluorometholone.

None of the disclosures of the art discussed before teaches or suggests that polycarbophil or a similar polymer can be used as a moisturizing agent in a composition for dry skin and mucosa as is disclosed hereinafter.

Summary of the Invention

The present invention contemplates a composition and method of moisturizing skin and mucosa. In accordance with the method, an effective moisturizing amount of a moisturizing composition that consists essentially of a moisturizing amount of a bioadhesive, water-swellable, but water-insoluble, particulate, fibrous cross-linked carboxy-functional polymer is used to contact the skin or mucous membrane of a mammal such as a human. The polymer contains (a) a plurality of repeating units of which at least about 80 percent, and preferably at least about 90 percent, contain at least one carboxyl functionality, and (b) about 0.05 to about 1.5 percent, preferably about 0.1 to about 1.0 percent, cross-linking agent that is substantially free from polyalkenyl polyether, based upon the weights of unpolymerized starting materials; i.e., r p ating units and cross-linking agent. That contact is maintained for a time period sufficient to moisturize the contacted skin or mucous membrane.

In preferred practice, the dry bioadhesive polymer is sized to pass through a 400 mesh sieve screen, U.S. Standard Sieve Series. It is also preferred that the bioadhesive particle be dispersed in a physiologically tolerable diluent, and particularly a liquid that includes water.

Brief Description of the Drawings

In the figures forming a part of this disclosure,

Figure 1 illustrates a diagrammatic side view of a modified, commercially available surface tensiometer utilized to measure adhesive strength of bioadhesives;

Figure 2 is a graph illustrating the force (dynes x $10^{-2}/cm^2$) for detaching a bioadhesive polymer reaction product of acrylic acid copolymerized with 0.3 weight percent 3,4-dihydroxy-1,5-hexadiene having a density of 1.56 grams/cubic centimeter (g/cc) versus pH value.

The present invention provides several advantages and benefits.

One advantage of the present invention is that its compositions are not noticeably irritating to the skin or mucosa with which they are contacted.

One of the salient benefits of the present invention is that its moisturizing effects can be relatively long lasting because of insolubility.

Yet another benefit of the present invention is that its compositions can be fabricated with relative ease.

Still further benefits and advantages of the present invention will be apparent to those skilled in the art from the Detailed Description, Examples and claims that follow.

Detailed Description of the Invention

The present invention relates to a method of moisturizing skin or a mucous membrane area by administering a moisturizing composition to a host mammal. The compositions themselves consist essentially of a moisturizing effective amount of a bioadhesive moisturizing polymer.

The moisturizing composition is designed for use on the skin and mucous membranes (mucosa) of a mammalian animal body, such as that of a human, to which the composition adheres in the presence of a sufficient amount of water to swell the bioadhesive. The composition so adhered to mucosa or skin moisturizes the contacted body area for relatively long periods of time. Such time periods are longer than the time of moisturization for a similar composition that does not include a bioadhesive as disclosed herein. Indeed, for moisturization of mucosa, the bioadhesive moisturizer can remain in place and active for a time period of 10 to about 20 hours; i.e., the turn-over time for mucin or skin.

A composition useful in this invention is substantially non-toxic to the animals in which or on which it is placed. Thus, when contacted with and adhered to skin or mucosa, a composition causes no apparent whitening or blistering effects due to the bioadhesive, as is reported in U.S. Patent No. 4,226,848. In addition, adverse immunologic effects from the use of such compositions in and on animals have not been noted.

The method of the present invention utilizes a hydrogel composition that holds substantial quantities of water in contact with the skin or mucosal area of a host mammal for extended periods of time. This composition functions additionally as a polyelectrolyte and restricts ion efflux from the contacted mucous membrane. Such ion efflux can cause water to move out of tissues. Further, the moisturizing bioadhesive when swollen by an aqueous medium is itself a polyelectrolyte, and produces a Donnan equilibrium effect, resulting in the facilitation of ion influx into the contacted mucosal tissue. This composition is retained in contact with the skin or mucosal tissue for extended periods of time in the method of the present invention as a result of the substantial bioadhesive, and mucoadhesive, properties of the cross-linked polymer.

The method of moisturizing of the present invention is effective for moisturizing several "dry" tissues, such as dry eye, dry skin, dry vagina, dry nasal passage, dry rectal passage and dry mouth. The art has not recognized a singular objective assay for dry skin or mucous membrane, but certain features are usually noted clinically. One is a lack of pliancy and a flaking that is noted on rubbing. A second is itching and pain of the affected area. A third is a relative lack of plumpness of the affected cells relative to "normal" cells. The cells of such a dry area are typically damaged by usually used cytological or tinctatorial assays.

In accordance with this method of moisturizing, a composition containing a moisturizing effective amount of a moisturizing bioadhesive polymer is provided, as described before. An area of skin or mucous membrane to be moisturized is contacted with the provided composition. The contact is carried out in the presence of sufficient water to swell the bioadhesive and cause the bioadhesive-containing composition to adhere to the area contacted.

Each of the hereinafter-described compositions can be administered in accordance with this method.

A composition useful in this invention can be administered by several means to provide the desired contact between the skin or mucous membrane and the composition. For example, the composition can be applied to the skin by rubbing the composition over the skin area to be moisturized. Where the conjunctival mucosa are to be contacted, the aqueous composition described hereinafter can be instilled into the precorneal pockets of the eyes. Where the buccal, nasal, anal and/or vaginal mucosa are to be contacted, the composition can be applied by spray, hand, forceps, suppository, douche or other suitable instrument.

The composition is left in place (contact maintained) for a time sufficient for moisturization of the affected area to occur and thereby provide its cosmetic function to the animal. In most circumstances, the administered composition is eliminated from the body by a natural bodily mechanism, such as by dispersion or erosion caused mechanically or by an aqueous body fluid such as saliva, tears, or vaginal secretions, or by washing.

More specifically, when applied to the skin, the moisturizing polymer contacts the upper (outer) skin layer or stratum corneum and adheres thereto bioadhesively. The moisturizing bioadhesive polymer remains in place until it is rubbed off by the mechanical action of a person's clothes, the agent(s) adhered to stratum corneum cells are sloughed off, the user washes the polymer off with a dispersing agent such as soap or detergent, or the like. For mucosa, a bioadhesive moisturizing polymer adheres to the mucin that covers the membrane or to the membrane itself. Mucin is replaced (turns over) within about 10 to about 20 hours, usually about every 17 hours, and the adhered bioadhesive moisturizing polymer is lost with the mucin. The bioadhesive moisturizing polymer can also be lost by mechanical action at the site of contact, as by action of the eye lid on the eyeball or tongue in the buccal cavity. Other modes of loss can also occur such as washing as are appropriate to the site of contact.

The principal moisturizing ingredient of a composition of this invention is a bioadhesive polymer. The composition consists essentially of the bioadhesive polymer, by which it is meant that although ingredients such as water and adjuvants or diluents can be present, other ingredients that materially alter the basic and novel characteristics of the bioadhesive polymer or a before-described moisturizing composition are absent.

Exemplary of such other ingredients that are absent from the present compositions are the treating agents that are disclosed in U.S. Patents No. 4,615,697 and No. 4,795,436, which include medicinal agents and cosmetic agents. Thus, a moisturizing composition is free of treating agents, whether those agents are medicinal as is the case for drugs such as hormones, antidiarrheal agents and the like, or cosmetic such as sun screens, vitamins or minerals, keratolytic agents and the like.

This bioadhesive polymer comprises a water-swellable, but water-insoluble, particulate, fibrous, cross-linked carboxy-functional polymer. The polymer contains (a) a plurality of repeating units of which at least about 80 percent contain at least one carboxyl functionality and (b) about 0.05 to about 1.5 percent cross-linking agent substantially free from polyalkenyl polyether, with the percentages being based upon the weights of unpolymerized repeating unit and cross-linking agent, respectively. In more preferred practice, at least about 90 percent of the repeating units contain at least one carboxyl functionality, and in still more preferred practice, at least 95 percent of those repeating units contain at least one carboxyl functionality. Most preferably, the bioadhesive is a reaction product of the polymerization of only a single carboxyl-functional monomer and the cross-linking agent. Also in more preferred practice, the bioadhesive contains about 0.1 to about 1 percent by weight of polymerized cross-linking agent.

A bioadhesive can be broadly defined as a material that adheres to a live or freshly killed biological surface such as mucous membrane or skin tissue. Bioadhesion, as that phrase is used herein to define a useful bioadhesive moisturizing polymer, is assayed by a procedure described hereinafter in Example 2 that measures the force required to separate two layers of freshly excised rabbit stomach tissue that are adhered together by an adhesive. Using this procedure, a bioadhesive can be defined as a material that requires a force of at least about 50 dynes/cm^2 to separate two adhered, freshly excised pieces of rabbit stomach tissue, following the procedure of Example 2. Upper limits for forces required to separate the freshly excised rabbit tissue are presently unknown, but are believed to be at least about 2000 dynes/cm^2.

For purposes of comparison, a non-bioadhesive, cross-linked, strongly acidic macromolecular and swellable polymer having sulfonic acid functionality such as the cation exchange resin sold by Rohm and Haas, Company of Philadelphia, Pennsylvania as its AMBERLITE® 200 exchange resin requires almost no force to separate the excised tissue, while homopoly(2-hydroxyethyl methacrylate) requires a force of about 29 dynes/cm^2 for separation.

As noted previously, at least about 80 percent of the repeating units of the bioadhesive contain at least one carboxyl functionality. Exemplary monomers that provide these repeating units are monoethyl nically unsaturated and include acrylic acid, methacrylic acid, fumaric acid, maleic acid, maleic anhydrid which may be hydrolyzed into its acid form during or aft r polymerization, itaconic acid, crotonic acid, and the

like. Each of these acids can be used alone or in combination with other such acids or with one or more pharmaceutically or cosmetically acceptable salts of those acids. Acrylic acid is a particularly preferred monomer for providing the repeating units of the bioadhesive polymer.

The bioadhesive polymers useful in this invention are cross-linked by cross-linking agents as are known in the art. The cross-linking agent is substantially free from polyalkenyl polyethers, and is particularly free from polyalkenyl polyethers such as polyallyl sucrose or polyallyl pentaerythritol containing an average of at least three allyl groups per molecule as are reportedly present in CARBOPOL® 934. Exemplary of useful cross-linking agents are divinylbenzene, N,N-diallylacrylamide, 3,4-dihydroxy-1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene and the like.

The amount of cross-linking of the bioadhesive is of some import. When less than about 0.05 weight percent of an appropriate cross-linking agent is present, the bioadhesive tends to become water-soluble, or water-dispersible, thereby losing its desired water-insoluble, water-swellable, fibrous character that is important to the invention. When greater than about 1 percent cross-linking agent is present, the water-swellability of the bioadhesive begins to decrease appreciably. At cross-linking agent levels greater than about 1.5 percent, the water-swellability is sufficiently decreased so as to make the bioadhesive lose its desired, functional characteristics. Preferably, the cross-linking agent is present at about 0.1 to about 1 percent.

The above amounts of carboxy-functional repeating units and cross-linking agent are used to define the bioadhesive, but specifically refer to the percentages of those predecessor, unpolymerized monomers in the reaction mixture from which the bioadhesive is polymerized. These pre-polymerization amounts are utilized because of the great difficulty in analyzing the polymerized bioadhesive. Although the amounts refer to the pre-polymerized monomers, it is believed that the bioadhesives contain substantially similar amounts of those monomers in polymerized form.

A bioadhesive polymer useful herein can thus be in part defined as a reaction product of the copolymerization of at least 80 weight percent monoethylenically unsaturated carboxy-functional monomer and about 0.05 to about 1.5 weight percent of a cross-linking agent free of polyalkenyl polyether. The remaining monomers that can be present to constitute 100 percent by weight of the monomers are discussed below.

In addition to the above two ingredients, the bioadhesive polymer can also include polymerized monoethylenically unsaturated repeating units such as C_1-C_6 alkyl esters of one or more of the above-described acids such as hexyl acrylate, butyl methacrylate and methyl crotonate; hydroxyalkylene-functional esters of the above-described acids that contain a per molecule average of 1 to about 4 oxyalkylene groups containing 2-3 carbon atoms such as hydroxyethyl methacrylate, hydroxypropyl acrylate and tetraethylene glycol monoacrylate; methacrylamide, acrylamide and their C_1-C_4 mono- and di-alkyl derivatives such as N-methyl acrylamide, N-butyl methacrylamide and N,N-dimethyl acrylamide; styrene; and the like as ar known in the art as being copolymerizable with the above described carboxyl functionality-containing monomers and cross-linking agents. The bioadhesive polymers most preferably are prepared from only the monoethylenically unsaturated carboxy-functional monomer and the cross-linking agent.

A bioadhesive moisturizing polymer useful herein can be prepared by conventional free radical polymerization techniques utilizing initiators such as benzoyl peroxide, azobisisobutyronitrile, and the like, is polymerized in an aqueous medium, and is not agglomerated by steam action. Exemplary preparations of useful bioadhesives are provided hereinafter and can also be found in U.S. Patents No. 2,810,716 and No. 3,202,577, whose disclosures are incorporated herein by reference.

The polymers described in U.S. Patent No. 3,202,577 are reported therein to be useful in treating diarrheal states. The disclosures of that patent are directed to the use of its polymers as bulking or dehydrating agents, and not as bioadhesives.

A polymer similar to those of U.S. Patent No. 2,810,716 or No. 3,202,577 is used in commercial form as a calcium salt and is available generically as calcium polycarbophil in chewable tablet form. Such a polymer appears to be produced in accordance with U.S. Patent No. 3,297,664 and is not contemplated herein.

The bioadhesive useful herein is fibrous or particulate, and swellable in water, but is insoluble in water. Thus, the bioadhesive useful herein can be distinguished from those polymers of U.S. Patents No. 3,074,802, No. 3,330,729 and No. 4,226,848, described hereinbefore that utilize CARBOPOL® 934. That polymer does provide adhesion as discussed herein, but is water-soluble, making it less desirable, and is therefore excluded from the bioadhesives of this invention. Thus, CARBOPOL® 934 is said in U.S. Patent No. 4,226,848 to be sufficiently water-soluble to provide a measurable viscosity at a concentration of 0.2 p rcent by w ight in water. Contrarily, as illustrated h reinafter in the examples, the bioadh siv s us ful herein are pr pared in aqueous solution and separate therefrom after polymerization.

In addition, the polymers of U.S. Patents No. 3,074,852, No. 3,330,729 and No. 4,226,848 ar cross-linked by a polyalkenyl polyether such as the triallyl ether of sucrose or the triallyl ether of pentaerythritol. The bioadhesives of the present invention are substantially free of such cross-links, particularly of cross-links by agents having an average of at least about three allyl groups per molecule.

N verthel ss, the fibrous, bioadhesive polymers of this invention are sw llabl in water; i.e., the polymer particles sorb water (adsorb or absorb) and thereby become larger in size in the presence of water. The water used for that swelling, can be that provided along with the composition of the present invention or it can be that provided by the body of the treated animal, such as by moisture transpiration or secretion through the skin, by mucosal secretions such as saliva, or by secretion of tears in the eye.

The size of the bioadhesive particles has an effect upon the compositions of this invention. It is apparent that the bioadhesive particles should not be so large that the composition cannot be administered without undue difficulty. Similarly, particles sized larger than those discussed below can sometimes cause pain and irritation when administered for ocular, buccal or vaginal use. In addition, it appears as though particles sized as discussed below provide improved function to the moisturizer composition as compared to particles that are larger in size; i.e., in the longest dimension.

Typically, at the maximum, a useful bioadhesive polymer is sized to pass through a sieve screen having a 400 mesh (U.S. Standard Sieve Series); i.e., a 38 micron opening. Preferably, the bioadhesive polymer particles are smaller still and are sized so that the longest dimension is about 20 microns. Most preferably, the particles have a number average size of about 2 microns to about 5 microns in the longest dimension. Although the last named particle size is particularly preferred for ophthalmic uses, those smallest sized particles are also useful in any composition described herein. Particles of a desired size can be obtained, for example, by grinding, crushing or otherwise comminuting larger particles.

Particles having a relatively small size have a greater surface area per unit weight, swell more rapidly, and appear to adhere better than do particles having a relatively large size, and thus, a relatively small size is preferred for the particles. Bioadhesion measurements discussed before and in Example 2 hereinafter are carried out for convenience using a bioadhesive sized to pass through a 30 mesh sieve screen and be retained on a 40 mesh sieve screen (U.S. Standard Sieve Series); i.e., 30/40 mesh size.

Bioadhesion has not been found to be a function of the molecular weight of the bioadhesive. Consequently, the bioadhesive can be of substantially any molecular weight, so long as its adhesion in the adhesion test described hereinafter is at least about 50 dynes/cm^2.

As noted previously, the bioadhesives are polymerized in an aqueous medium. In preferred practice that aqueous medium is a saturated solution of an alkaline earth metal salt such as magnesium sulfate. The alkaline earth metal salt serves at least two functions. First, it increases the density of the polymerization medium so that the polymerized bioadhesive floats on the surface of the aqueous medium and can be easily removed therefrom. Second, the use of magnesium sulfate, in particular, reduces the swelling of the bioadhesive in the aqueous medium so that polymerization and recovery are facilitated. Bioadhesives so prepared typically contain about 0.5 to about 1 percent of the alkaline earth metal ion after several water rinsings of the polymer. These polymers thus differ from those in which an alkaline earth metal hydroxide is used to neutralize the carboxyl groups as in calcium or magnesium polycarbophil.

Particularly preferred bioadhesives that are commercially available are those materials sold under the designation polycarbophil by A. H. Robins Co. of Richmond, Virginia. and "EX55" by B.F. Goodrich Chemical Co. of Cleveland, Ohio, the manufacturer of CARBOPOL® 934 that is also discussed herein. The United States Pharmacopeia (U.S.P.) 1980 ed., United States Pharmacopeial Convention, Inc., Rockville, Maryland, at page 638, indicates that polycarbophil is a polyacrylic acid cross-linked with divinyl glycol that has a residue on ignition of less than 4.0 percent and absorbs about 60 times it original weight in test B under Absorbing power. The 1985 edition of the U.S.P. lists only calcium polycarbophil that contains 18-22 percent calcium and is different from the material described in the 1980 edition.

The material designated as "EX55" from the B. F. Goodrich Co., above, sorbs (absorbs and adsorbs) about 40 to about 60 times its weight of water. That sorption value is similar to the sorption capacity of natural mucin. A useful bioadhesive is also a polyanionic polymer with a charge density similar to mucin.

Useful bioadhesive polymers of this invention were examined as to their densities, which are typically about 1.30-1.70 grams/cubic centimeter (g/cc). The cross-linking percentage was found to have a small effect upon the resulting density of illustrative, synthesized polymers as is shown in the Table below. Also shown in that Table is a somewhat greater effect upon density that is observed for diff rent starting monomers.

Densities of Useful Bioadhesives			
Bioadhesive		%-CL[1]	Density[2] (g/cc [3])
Monomer	Cross-linker		
acrylic acid	3,4-dihydroxy-1,5-hexadiene	0.05	1.49
acrylic acid	3,4-dihydroxy-1,5-hexadiene	0.30	1.56
acrylic acid	3,4-dihydroxy-1,5-hexadiene	0.60	1.57
acrylic acid	3,4-dihydroxy-1,5-hexadiene	1.20	1.62
acrylic acid	3,4-dihydroxy-1,5-hexadiene	2.00	1.65
methacrylic acid	2,5-dimethyl-1,5-hexadiene	0.30	1.47
methacrylic acid	divinyl benzene	0.30	1.36

[1] %-CL = weight percent cross-linking agent based upon total polymerizable monomers.

[2] Density of each polymer was determined in a 2 milliliter specific gravity bottle at 25 C. Benzene of known density (0.874 g/cc) was used at the medium.

[3] g/cc = grams per cubic centimeter.

The bioadhesive moisturizing agent is present in the compositions of this invention in an amount that is sufficient to provide moisturization for a desired period of time for which the composition of this invention is to be administered, and such an amount is referred to herein as "an effective moisturizing amount". As is well known, effective amounts of agents vary with the particular agent employed, the condition being treated and the rate at which the composition containing the agent is eliminated from the body, as well as varying with the animal in which it is used. Consequently, effective amounts of moisturizing agents can not be defined for each agent. Thus, an effective moisturizing amount is that amount, which in a composition of this invention, provides a sufficient amount of the moisturizing agent to provide the requisite moisturization on the body of the treated animal for the desired period of time. An effective amount can therefore also be defined as a moisturizing amount.

As there is no universally accepted assay for dry skin or mucosa, there also is no universally accepted assay for moisturized skin or mucosa. Both conditions are usually determined subjectively by the person who has dry or moisturized skin or mucosa and by clinicians skilled in making such evaluations.

Nevertheless, some criteria for moisturized skin and mucosa include a pliant, non-flaky surface, an absence of itching, and a relative plumpness of the cells of the treated area. Relative plumpness can be examined by scanning electron microscopy of casts made from the treated areas.

In addition, dry eye conditions are typically associated with tissue damage. Such damage can be assayed by staining techniques such as with fluorescein dye. Thus, moisturization of the mucosa of the eye can be assessed by the relative amount of staining with a dye such as fluorescein of one group of subjects with a dry eye condition without treatment by a method of the invention as compared with the staining observed in a similar group of subjects that have been treated according to a method of the invention.

Several workers have tried to quantify dry and moisturized skin by various techniques. For example, Leveque et al., J. Soc. Cosmet. Chem., 34:419-420 (Dec. 1983) have reviewed in vivo impedance methods for such assays. Potts, J. Soc. Cosmet. Chem., 37:9-33 (Jan./Feb. 1986) reviewed several techniques for both in vivo and in vitro measurements of stratum corneum hydration. Lieb et al., J. Soc. Cosmet. Chem., 30:107-119 (March/April 1988) discuss an in vitro method for measuring transepidermal water loss (TEWL). In the latter paper, oleaginous materials such as mineral oil that form an occlusive layer over the skin tend to lower TEWL, whereas humectant materials such as glycerin in water raised the TEWL values.

Although none of the methods discussed in any of the above papers is universally accepted or applicable, a TEWL method such as that described by Lieb et al. for humectant-type materials appears to be useful for the bioadhesive moisturizing polymers herein when quantitative data are required. Otherwise, the expertise of trained observers and/or comments of clinical subjects are sufficient assays for a useful moisturizing method as discussed herein.

A moisturizing composition utilized in th method of the present invention is designed to provide about 0.25 grams to about 15 grams (g) of bioadhesive per 100 milliliters (about 0.25 to about 15 weight percent) of the composition. Mor preferably, a bioadhesive polymer is present at about 2 to about 5 grams per 100 ml of composition (about 2 to about 5 weight percent). The moisturizing water can be provided by the composition or by the contacted skin or mucosa, or both. Thus, the bioadhesive moisturizing agent can be dispersed and pre-swollen in an aqueous medium prior to application, or can be applied dry and free of

water or can be applied dispersed in a vehicle that contains enough water to partially hydrate the bioadhesive moisturizing agent particles.

A useful aqueous composition can have the consistency of a pourable liquid to a gel, with the consistency being a function of relative amounts of water, bioadhesive moisturizing polymer, osmoticity and the pH value of the composition formed. A relatively low amount of the polymer in a given amount of water produces a relatively thinner composition than does a greater amount of the polymer, with the pH value being held constant at both concentrations.

The pK_a of a useful bioadhesive moisturizing polymer is about 3. As a consequence, where a composition is at a pH value of about 5 or greater, substantially all of the acidic protons are neutralized and the polymer-containing composition exhibits its thickest consistency for that concentration. On the other hand, at pH values such as 2, below the polymer's pK_a value, the composition is relatively thinner, for a given concentration.

In addition, osmoticity of a composition can also play a role in the viscosity of the composition. Typically, higher solute concentrations decrease the viscosity of a composition when the amounts of bioadhesive polymer, water and the pH value are kept constant. Thus, the viscosity of a before-discussed composition having a pH value in excess of 5 can be reduced from that of a ringing gel to a pourable liquid by increasing the osmoticity of the composition.

An isotonic product has an osmoticity of about 280 to about 320 mOsM, and such an osmoticity is useful herein. The osmoticity of a moisturizing composition can be as high as about 450 to about 500 mOsM.

Pharmaceutically acceptable electrolytes and non-electrolytes, collectively referred to as solutes, are used for adjusting osmoticity and viscosity of a useful composition. Exemplary pharmaceutically acceptable electrolytes include sodium chloride, potassium chloride, sodium phosphate, potassium phosphate, sodium and potassium sulfates, and sodium and potassium bicarbonates. Exemplary pharmaceutically acceptable non-electrolytes include glycerin, sugars such as glucose and sucrose, sorbitol and urea. Thus, those solutes that are well known for adjusting osmolarity or osmolality are useful herein.

Osmoticity of a given composition is a measured value that is obtained using a vapor phase osmometer.

Thus, a composition containing a bioadhesive moisturizing polymer at or near the high end of the before-discussed concentrations and at a pH value of about 5 or greater exhibits more gel-like properties. Such compositions can, nevertheless, be extruded in the form of drops from an eye dropper, particularly where sufficient electrolyte or other solute is present to raise the osmoticity to near about 450 mOsM. Conversely, a composition at or near the low end of the before-discussed concentrations and at a pH value below about 3 typically behaves as a pourable liquid unless a large amount of bioadhesive polymer is present.

In specific examples, a composition for vaginal moisturization can exhibit a viscosity of about 4,000 to about 40,000 cps at 25 degrees C, whereas a composition for buccal moisturization can exhibit a viscosity of about 1 to about 4,000 cps at 25 degrees C. The thicker compositions typically exhibit non-Newtonian flow characteristics. The viscosity of such solutions is therefore measured with a viscometer that is especially designed for such compositions. The viscometer utilized for the viscosity measurements discussed herein is a commercially available Haake ROTOVISCO Model RV-12, available from Haake, Inc., 244 Saddle Brook Road, Saddle Brook, NJ 07662. The machine utilized an SV cup and an SVII rotor for determining viscosity in centipoises (cps) at shear rates of 1-8 revolutions per minute (rpm) and at a temperature of 25 degrees C.

With the above extremes of consistency in mind, a skilled worker can readily formulate a moisturizing composition having a desired consistency. It should also be understood that the pH value of a moisturizing composition can change once the composition is contacted with the skin or mucosa as a result of the local pH value of the area to which the composition is applied.

The moisturizing bioadhesive is applied to the skin or mucosa in an amount sufficient to form a layer of hydrated bioadhesive particles that is substantially continuous over the applied surface. Typically, that layer is several particles thick. In terms of the dry bioadhesive moisturizing agent, the bioadhesive moisturizing agent is applied in an amount of about 1 to about 50 milligrams (mg) per square centimeter (cm^2) of contacted skin or mucosa.

The amount applied is also a function of the location of the application. For example, application to the y r quires a relatively small amount of total moisturizing composition due to possibl discomfort that can aris wh n any foreign material is in the eye. Conversely, application to th skin and vaginal mucosa can be in excess of that needed to provide moisturization.

For example, about 0.025 to about 1.0 mg/cm^2 of moisturizing polymer (about 25 to about 50 microliters of a composition containing about 1 to about 3 weight percent of the polymer) are used for eye moisturizing compositions, whereas about 10 to about 50 mg/cm^2 of moisturizing polymer are used for moisturizing skin.

For application to the buccal, nasal, rectal and vaginal mucosa, it is more convenient to refer to the amount of bioadhesive moisturizing polymer applied in terms of the total weight of the polymer applied. Thus, for the buccal mucosa, a composition containing about 0.25 to about 5 weight percent of the bioadhesive moisturizing polymer is applied. For the vaginal mucosa, the amount of composition is about 1 to about 5 grams of a composition containing about 0.25 to about 3 weight percent of the bioadhesive polymer. This latter amount is in excess of that needed for moisturization, but the excess is useful in providing lubrication during sexual intercourse. Broadly, then, a liquid composition contains about 0.25 to about 5 weight percent bioadhesive polymer or moisturizing agent.

In addition to the bioadhesive polymer moisturizing agent, a composition useful in this invention can also contain one or more pharmaceutically or cosmetically acceptable additives that are referred to herein as adjuvants that assist in providing shelf life and customer acceptance of a moisturizing product. Exemplary adjuvants include preservatives, emollients, lubricating oils, emulsifying agents, thickeners, humectants, coloring agents, and odor providing agents (odorants).

The phrases "pharmaceutically acceptable", "cosmetically acceptable" or "physiologically tolerable" are used herein to mean that the material so described can be used for treatments in or on humans or other mammals without causing ill effects, such as toxicity, blistering or whitening of mucosa or skin tissues, and that those materials are not themselves bioadhesive moisturizing agents, as those words are used her in. Exemplary adjuvants can be found in Chapter 67 of Remington's Pharmaceutical Science, 16th ed., Osol et al. eds, Mack Publishing Company, Easton, PA (1980).

It is noted that the above-mentioned adjuvants can be present in an amount that is greater than the bioadhesive polymer. Even though such can be the case, the adjuvants do not provide the moisturization of the composition, but rather provide emulsification or lubricity or the like, and typically assist in application of the compositions. This is the case where a compound such as glycerin or sorbitol that is a known humectant is present since such materials are water-soluble, non-bioadhesives that are typically lost with perspiration or the like. Similarly, lubricating oils and emulsifying agents provide lubricity to a vaginal moisturizer for sexual intercourse.

A moisturizing composition useful herein can be applied to contact the skin or mucosa as a dry powder, an aqueous suspension or a non-aqueous suspension. That application can be in the form of a spray of the powder or a suspension, to drops, to a composition having a cream or gel-like consistency.

In one embodiment, the dry bioadhesive moisturizing polymer is swollen in an aqueous medium at a desired pH value, and then applied to contact the desired tissue such as the eye. The word "dry" is used herein in relation to a bioadhesive moisturizing polymer to mean that the polymer does not adhere when touched with a finger within a rubber glove, and is substantially unswollen.

A bioadhesive can also be employed with suppositories for rectal or vaginal administration, in which case the bioadhesive polymer is dispersed therein. A thin aqueous dispersion of bioadhesive moisturizing particles is also useful as a vaginal or rectal douche. A gel-like consistency is preferred for a vaginal moisturizer, with the composition being applied by means of a plunger-type applicator as is well known for use in applying vaginal products.

In another illustrative embodiment, the bioadhesive moisturizing agent is intimately mixed in an pharmaceutically acceptable aqueous carrier as diluent for use in an eye. The bioadhesive is preferably comminuted or otherwise sized to a number average size of about 2 to about 5 microns in the longest dimension for use in the eye. The composition so prepared can then be instilled as drops in the precorneal pocket of the eye to contact the conjunctival surface, and thereby provide contact of the moisturizing composition to that mucous membrane.

Best Modes For Carrying Out The Invention

Example 1: Bioadhesive Polymer Preparation

Bioadhesive polymers useful herein were prepared following the general synthetic procedure discussed immediately below. Specific bioadhesive polymers made in accordance with the general procedure are illustrated in Table 1, hereinaft r.

A solution containing 100 millilit rs of distilled water and 800 grams of magnesium sulfat ($MgSO_4$-$7H_2O$) was heated to reflux with agitation. A mixture of 1 gram of initiator dissolv d in 100 grams of monomeric carboxy-functional repeating unit and the amount of cross-linking ag nt shown in Table 1 was

added to the refluxing aqueous solution with continued stirring. The polymerizing composition so prepared was agitated and heated to the temperature shown in Table 1 for the period of initial polymerization and of post-polymerization curing.

At the termination of the curing time, the polymerized composition was diluted with 150 milliliters of distilled water heated to a temperature of about 95 C and then strained through a stainless steel sieve having a 40 mesh screen (U.S. Standard Sieve Series). The strained bioadhesive remaining on the screen was washed with one 1 liter portion of water heated to a temperature of about 80 C followed by five separate 1 liter washings using tepid water. The washed bioadhesive so prepared was then dried in a forced air oven at a temperature of 90 C for a period of 48 hours.

The bioadhesives so prepared were then used as such or comminuted and sieved to provide a desired particle size.

Table 1
Bioadhesives

Carboxy-functional Repeating Unit[1]	Cross-Linking Agent[2]	Initiator[3]	Polymerization Conditions: Poly. Time[4]	T.[5]	Time[6]	Yield[7]
(A)	(a) 0.2	(1)	15	95	2	83
(A)	(b) 1.0	(1)	25	95	18	67
(B)	(a) 1.0	(1)	30	95	48	53
(B)	(b) 1.0	(1)	30	95	48	87
(C)[8]	(a) 1.0	(1)	--	65	24	11
(D)[8]	(a) 0.2	(2)	20	95	72	10
(A)	(c) 0.2	(1)	10	95	4	98
(B)	(c) 0.2	(1)	10	95	20	93

[1] 100 Grams of each of the following carboxy-functional repeating units was used: (A) = acrylic acid; (B) = methacrylic acid; (C) = itaconic acid; and (D) = maleic anhydride.

[2] The numerals of the Table indicate the number of grams of the particular cross-linking agent used. The particular cross-linking agents were: (a) = 3,4-dihydroxy-1,5-hexadiene; (b) = divinyl benzene; and (c) = 2,5-dimethyl-1,5-hexadiene.

[3] One gram of the following initiators was used: (1) = benzoyl peroxide; and (2) = azobisisobutyronitrile.

[4] Initial polymerization time in minutes.

[5] Temperature in degrees C for initial polymerization and post-polymerization cure.

[6] Post-polymerization cure time in hours.

[7] Yield of dried bioadhesive based upon the weights of starting materials and recovered bioadhesive.

[8] A nitrogen sparge was used during polymerization as was deaerated distilled water prepared by boiling distilled water for a period of 10 minutes.

Although optimization of polymerization conditions is not reflected in the data of Table 1, it can be seen from those data that the bioadhesives useful herein are easily prepared in useful quantities. It is noted that the first bioadhesive listed in Table 1 has bioadhesion and other physical and chemical properties that are substantially identical to the commercially available bioadhesive sold under the designation polycarbophil by A.H. Robins Co. of Richmond, Virginia. as well as that sold under the designation EX55 by B.F. Goodrich

Chemical Co. of Cleveland, Ohio.

Example 2: Measurement of Adhesion

As noted previously, a bioadhesive moisturizing polymer of this invention is a water-insoluble, but water-swellable, particulate, fibrous, cross-linked carboxy-functional polymer that contains specified amounts of carboxyl functionality and cross-linking agent. In addition, to that chemical definition, a useful bioadhesive by definition must also exhibit an adhesion between two pieces of freshly excised rabbit stomach tissue of at least about 50 dynes/cm^2 when measured under specified conditions. Those conditions and the apparatus utilized for that measurement are described hereinbelow.

The apparatus utilized for these measurements is illustrated in Figure 1. Basically, the apparatus is a standard, surface tensiometer as is available from Biolar Corporation, of North Grafton, Massachusetts that has been modified by removal of the du Nuoy loop and its replacement by an elongated linking arm 48 and an excised stomach tissue holding means 44.

Fresh stomach was obtained from rabbits and was carefully washed with a chilled solution containing 0.9 weight percent sodium chloride in distilled water (normal saline solution) to remove the contents. The stomach was placed in an aerated, chilled normal saline solution until used.

The tissue was cut into a round shape from the fundus part of the stomach and secured mucosal side out over a weighted container such as a 15 milliliter scintillation vial using a rubber band, as indicated by the reference numeral 40 of Figure 1. The container 40 was placed into a 500 milliliter beaker 42 containing gastric fluid. The beaker 42 was placed under the scale portion of the modified tensiometer as illustrated in Figure 1.

A separate portion of excised stomach tissue was separated into two layers of smooth muscle; i.e., the external longitudinal layer and the internal circular layer. A piece of the internal circular layer was placed mucosal side out over a No. 2 rubber stopper, and the tissue was secured to the rubber stopper using an aluminum vial cap having a uniform-sized opening of about 0.78 square centimeters. The aluminum vial cap is available from Wheaton Company of Millville, New Jersey. A holding means in the form of screw eye was inserted into the opposite end of the rubber stopper from that to which the tissue was secured. The rubber stopper containing the holding means and affixed tissue was placed in an aerated, chilled normal saline solution until used.

One hundred microliters of gastric fluid was added to 4 milligram samples of each polymer whose bioadhesion was to be measured. One hour after that addition, the swollen polymer was carefully spread over the tissue on the rubber stopper. Any excess of fluid was removed from the polymer by blotting with a tissue paper. The rubber stopper with holding means, tissue and polymer 44 was suspended from the scale so that it rested in the beaker of gastric fluid. When the polymer layer was at a depth equal to that of the tissue already in the container on vial 40, the scale was adjusted to zero using appropriate weights. The rubber stopper with holding means, tissue and polymer 44 was then suspended over the tissue on the weighted container 40, and that container 40 was elevated to contact the polymer using the elevation means 46. Care was taken to assure that the tissue on the container 40 touched only the polymer.

The beaker was then slowly raised until the tissues came into contact, the contact being initiated by the weight of the rubber stopper (1.8 grams). After one minute, the weight was removed, and the force required to separate the polymer from the tissue was measured. The force exerted to separate the layers of stomach tissue was increased at a constant rate of 10 milligrams per second in weight until the tissues separated.

One measurement was carried out within five minutes of contact between the tissue and adhesive of rubber stopper 44 and the tissue of the vial 40. Excised stomach tissue was affixed to either the vial or rubber stopper within 30 minutes of sacrificing the rabbit and is thereby considered to be freshly excised tissue.

Exemplary results using the above measurement technique are illustrated for four useful bioadhesives in Table 2 hereinafter. The bioadhesives were prepared as described in Example 1 with the exception that 0.3 weight percent of cross-linking agent was utilized. After the preparation, the bioadhesives were sieved and dry particles having a 30/40 mesh size (U.S. Standard Sieve Series) were used for these measurements.

Table 2

Bioadhesion Measurements			
Polymer[1]	Weight to Separate Tissues[2]	Force to Separate Tissues[3]	Number of Measurements
1	855±55	1061±68	13
2	864±56	1072±68	12
3	876±57	1086±71	13
4	306±45	380±56	8

[1] Polymer 1 = polyacrylic acid cross-linked with 3,4-dihydroxy-1,5-hexadiene; polymer 2 = polyacrylic acid cross-linked with 2,5-dimethyl-1,5-hexadiene; polymer 3 = polyacrylic acid cross-linked with divinylbenzene; and polymer 4 = polymethacrylic acid cross-linked with divinylbenzene.

[2] Weights are in milligrams ± standard error of the mean (S.E.M.)

[3] Forces are reported in dynes/cm^2 ± S.E.M.

Using the above measuring technique, p-HEMA commercially available from Aldrich Chemical Co. of Milwaukee, Wisconsin, required a force of 29 dynes/cm^2 to separate the tissues, while AMBERLITE® 200 cationic exchange resin available from Rohm and Haas Co. of Philadelphia, Pennsylvania, required almost no force to separate the tissues.

Example 3: Bioadhesion as a Function of pH Value

The force measured to separate a bioadhesive polymer that is the reaction product of the polymerization of acrylic acid with 0.3 weight percent of 3,4-dihydroxy-1,5-hexadiene that had a density of 1.56 g/cc is shown in Figure 2. As is seen from the Figure, the maximum adhesion was observed at a pH value of about 5 to about 6. That maximum value was more than twice the adhesive force required for the separation at pH values of 0.46, 1.42 or 2.0. As is also seen, adhesion provided by that bioadhesive polymer was substantially reduced at pH value of 7. That reduction was statistically significant in a Student's t-test, p less than 0.01. Bioadhesive forces were measured as discussed previously in Example 2.

Example 4: Method of Moisturizing Dry Skin

A composition of dry polycarbophil (5 g, B. F. Goodrich EX55) sized to pass through a 400 mesh siev screen (U.S. Standard Sieve Series) and whose number average longest dimensions are less than about 20 microns, micro-silicate particles (3.75 g Syloid 244 FP, Davison Chemical Division, W. R. Grace & Co., Baltimore, Maryland), light mineral oil (50 ml), 95% ethanol (250 ml) and water (q.s. ad distilled deionized water 1000 ml) is prepared by admixture with agitation.

The composition so prepared is spread upon the dry skin surface in an amount of about 0.5-1 g per 20-30 cm^2 of skin to be moisturized, and allowed to adhere. The polymer composition adheres to the contact area and holds water in contact with the dry skin surface.

Example 5: Method of Moisturizing Dry Skin

A composition is prepared by admixing with agitation dry polycarbophil (5.00 g; B. F. Goodrich EX55) having a number average particle size of about 2 to about 5 microns and CARBOPOL® 934P (2.50 g), Syloid 244 FP (3.75 g) with light mineral oil (50.00 ml), 95% ethanol (250.00 ml), urea (100.00 g), methylparaben (1 g), propylparaben (0.5 g) and dilut d to 1000 ml with distilled, deioniz d water. The resulting composition has a smooth creamy texture.

This composition is utilized as described above in Example 4 for treating dry skin. The pr sence of the mineral oil and CARBOPOL® 934 in the composition improve its texture and make the composition mor lubrous when appli d to the skin.

Example 6: Method of Moisturizing Dry Vagina

A composition prepared from the dry polycarbophil (3 g) of Example 4, methyl paraben (0.2 g). propylparaben (0.03 g) and water (100 ml) is admixed and agitated, and adjusted to pH 2.4 with a solution of sodium citrate in HCl. The composition so prepared has a gel-like consist ncy.

About 4 g of the above composition are placed into a plunger-type applicator. The applicator and its contents are placed into the vagina of a post-menopausal woman presenting with dry vagina and vaginitis, and the plunger is depressed to expel the composition into the subject's vaginal cavity to thereby contact the vaginal mucosa. The composition so applied moisturizes the mucosa and also provides lubrication for sexual intercourse.

Example 7: Method for Moisturizing Dry Mouth

A composition prepared from the dry polycarbophil (2.0 g), of Example 4, sorbitol [NEOSORB® P100T (10 g, Roquette Corporation)], aspartame (0.06 g, NUTRASWEET®), lemon-vanilla flavoring (1.0 g), methylparaben (0.20 gm), propylparaben (0.03 g) and water (100 ml) is prepared by admixture and agitation, and adjusted to pH 2.5 with sodium citrate-HCl in HCl.

The composition is administered into the mouth to moisturize dry or desiccated tissue therein. A similar composition can be administered in several application forms, such as an aqueous spray, a gel, a chewable tablet, a dry powder, wafer, pastille, lozenge and an emulsion. The additional application forms are prepared by well known techniques and need only contain the bioadhesive moisturizing polymer of the above-listed ingredients.

Regardless of the form in which the composition is used, the bioadhesive polymer contacts the buccal membranous tissue and maintains water within the oral mucosa.

Example 8: Method of Moisturizing Dry Eye

Polycarbophil (B. F. Goodrich EX55) is dried, crushed and sieved to provide particles that pass through a 400 mesh sieve screen (U.S. Standard Sieve Series), and whose number average longest dimension is about 2-5 microns. A composition of those particles of polycarbophil (3.0 g) and water (100 ml) is prepared by admixture with agitation, and adjusted to about pH 5.5. An electrolyte is added with further agitation to provide a thickened liquid. That liquid is applied to the ophthalmic mucosa in an amount of about 0.025-0.05 ml with an eye dropper. The resulting contact with the ophthalmic mucosa is maintained until the treated subject requires another treatment as is evidenced by itching of the eye.

The foregoing is intended as illustrative of the present invention but not limiting. Numerous variations and modifications may be effected without departing from the scope of the invention, as defined in the claims.

Claims

1. A cosmetic method of moisturizing mammalian skin or mucous membrane comprising contacting mammalian skin or mucous membrane with an effective moisturizing amount of a composition that consists essentially of a bioadhesive, water-swellable, but water-insoluble, particulate, fibrous cross-linked carboxy-functional polymer that contains (a) a plurality of repeating units of which at least 80 percent contain at least one carboxyl functionality, and (b) a cross-linking agent that is substantially free from polyalkenyl polyether in an amount of from 0.05 to 1.5 percent (based upon the weight of unpolymerized repeating units and cross-linking agents); and
maintaining said contact for a time period sufficient to moisturize said contacted skin or mucous membrane.

2. The method according to claim 1 wherein said bioadhesive polymer particles are sized to pass through a 400 mesh size sieve, U.S. Standard Sieve Series, when dry.

3. The method according to claim 2 wherein said bioadhesive polymer particles have a number average longest dimension of from 2 to 5 microns.

4. The method according to any preceding claim wherein said bioadhesive polymer particles are dispersed in a physiologically tolerable diluent prior to said contacting.

Revendications

1. Procédé cosmétique d'hydratation de la peau ou de la muqueuse d'un mammifère, comprenant la mise en contact de la peau ou de la muqueuse d'un mammifère avec une quantité hydratante efficace d'une composition essentiellement constituée d'un polymère carboxylé réticulé fibreux, particulaire, bioadhésif, gonflable à l'eau, mais insoluble dans l'eau, qui contient (a) plusieurs motifs récurrents dont au moins 80% contiennent au moins une fonction carboxyle et (b) un agent de réticulation essentiellement dépourvu de polyalcényl-polyéther, selon une proportion de 0,05 à 1,5% (par rapport au poids des motifs récurrents non polymérisés et des agents de réticulation); et
   le maintien dudit contact pendant suffisamment longtemps pour hydrater ladite peau ou muqueuse mise en contact.

2. Procédé selon la revendication 1, dans lequel lesdites particules de polymère bioadhésif sont dimensionnées de façon à traverser un tamis de 400 mesh, normes U.S., une fois sèches.

3. Procédé selon la revendication 2, dans lequel lesdites particules de polymère bioadhésif ont une grande dimension moyenne en nombre de 2 à 5 microns.

4. Procédé selon l'une quelconque des revendications précédentes, dans lequel les particules de polymère bioadhésif sont dispersées dans un diluant physiologiquement tolérable avant ladite mise n contact.

5. Procédé selon la revendication 4, dans lequel ledit diluant physiologiquement tolérable est un milieu liquide.

6. Procédé selon la revendication 5, dans lequel ledit milieu liquide contient de l'eau.

7. Procédé selon l'une quelconque des revendications précédentes, dans lequel la composition comprend de 0,25 à 5% en poids dudit polymère bioadhésif, qui contient (a) plusieurs motifs récurrents dont au moins 90% contiennent au moins une fonction carboxyle et (b) de 0,1 à 1,0% dudit agent de réticulation.

8. Procédé selon la revendication 7, dans lequel ladite composition a une consistance analogue à celle d'un gel.

9. Procédé selon la revendication 8, dans lequel ladite composition est appliquée en une quantité suffisante pour apporter à la peau de 10 à 50 mg/cm^2.

10. Procédé selon la revendication 8, dans lequel la muqueuse vaginale est mise en contact avec de 1 à 5 grammes de ladite composition qui contient de 0,25 à 3% en poids dudit polymère bioadhésif.

11. Procédé selon la revendication 7, dans lequel ladite composition a la consistance d'un liquide coulable.

12. Procédé selon la revendication 11, dans lequel ladite composition est appliquée en une quantité suffisante pour apporter à la muqueuse oculaire de 0,025 à 1 mg/cm^2.

13. Procédé selon la revendication 11, dans lequel on met en contact la muqueuse buccale avec de 0,25 à 5% en poids dudit polymère bioadhésif.

14. Utilisation d'une composition bioadhésive comme hydratant cosmétique pour la peau ou la muqueuse d'un mammifère, ladite composition étant essentiellement constituée d' au et d'une quantité hydratante d'un polymère carboxylé réticulé fibreux, particulaire, gonflable à l'eau, mais insoluble dans l'eau, qui contient (a) plusieurs motifs récurrents dont au moins 80% contiennent au moins une fonction carboxyle et (b) un agent de réticulation essentiellement dépourvu de polyalcénylpolyéther, selon une proportion de 0,05 à 1,5% (par rapport au poids des motifs récurrents non polymérisés t de l'agent de réticulation).

15. Utilisation d'un polymère bioadhésif dans la fabrication d'une composition destinée au traitement thérapeutique des peaux ou des muqueuses sèches des mammifères, ladite composition étant essentiellement constituée d'eau et d'un quantité hydratante d'un polymère carboxylé réticulé fibreux, particulaire, gonflable à l'eau, mais insoluble dans l'eau, qui contient (a) plusieurs motifs récurrents dont au moins 80% contiennent au moins un fonction carboxyle et (b) un agent de réticulation ess ntiellement dépourvu de polyalcénylpolyéther, selon une proportion de 0,05 à 1,5% (par rapport au poids des motifs récurrents non polymérisés et de l'agent de réticulation).

16. Utilisation selon la revendication 15, dans laquelle ladite composition est telle que définie dans l'une quelconque des revendications 2 à 8.

5. The method according to claim 4 wherein said physiologically tolerable diluent is a liquid medium.

6. The method according to claim 5 wherein said liquid medium contains water.

7. The method according to any preceding claim wherein the composition comprises from 0.25 to 5 weight percent of said bioadhesive polymer, which contains (a) a plurality of repeating units of which at least 90 percent contain at least one carboxyl functionality, and (b) from 0.1 to 1.0 percent of said cross-linking agent.

8. The method according to claim 7 wherein said composition has a gel-like consistency.

9. The method according to claim 8 wherein said composition is applied in an amount sufficient to provide from 10 to 50 mg/cm^2 to the skin.

10. The method according to claim 8 wherein the vaginal mucosa are contacted with from 1 to 5 grams of said composition that contains from 0.25 to 3 weight percent of said bioadhesive polymer.

11. The method according to claim 7 wherein said composition has the consistency of a pourable liquid.

12. The method according to claim 11 wherein said composition is applied in an amount sufficient to provide from 0.025 to 1 mg/cm^2 to the mucosa of the eye.

13. The method according to claim 11 wherein the buccal mucosa are contacted with from 0.25 to 5 w ight percent of said bioadhesive polymer.

14. The use of a bioadhesive composition as a cosmetic moisturizer for mammalian skin or mucous membrane, said composition consisting essentially of water and a moisturizing amount of a water-swellable, but water-insoluble, particulate, fibrous, cross-linked carboxy-functional polymer that contains (a) a plurality of repeating units of which at least 80 percent contain at least one carboxy functionality, and (b) a cross-linking agent that is substantially free from polyalkenyl polyether in an amount of from 0.05 to 1.5 percent (based upon the weight of unpolymerized repeating units and cross-linking agent).

15. The use of a bioadhesive polymer in the manufacture of a composition for the therapeutic treatment of dry conditions of mammalian skin or mucous membrane, said composition consisting essentially of water and a moisturizing amount of a water-swellable, but water-insoluble, particulate, fibrous, cross-linked carboxy-functional polymer that contains (a) a plurality of repeating units of which at least 80 percent contain at least one carboxy functionality, and (b) a cross-linking agent that is substantially free from polyalkenyl polyether in an amount of from 0.05 to 1.5 percent (based upon the weight of unpolymerized repeating units and cross-linking agent).

16. The use according to claim 15 wherein said composition is as defined in any of claims 2 to 8.

Patentansprüche

1. Ein kosmetisches Verfahren zur Anfeuchtung bzw. Feuchthaltung der Haut oder Schleimhaut von Säugetieren, bei welchem die Haut oder Schleimhaut von Säugetieren mit einer zur Anfeuchtung bzw. Feuchthaltung wirksamen Menge einer Zusammensetzung in Kontakt gebracht wird, die im wesentlichen besteht aus einem bioadhesiven, wasserquellbaren, jedoch wasserunlöslichen, teilchenförmigen, faserigen, vernetzten, Carboxy-funktionellen Polymer, das enthält: (a) eine Vielzahl sich wiederholender Einheiten, von denen mindestens 80 Prozent mindestens eine Carboxyl-Funktion enthalten, und (b) ein im wesentlichen von Polyalkenyl-Polyether freies Vernetzungsmittel in einer Menge von 0,05 bis 1,5 Prozent (bezogen auf das Gewicht der unpolymerisierten, sich wiederholenden Einheiten und der Vernetzungsmittel); und
Aufrechterhaltung dieses Kontakts während eines zur Anfeuchtung bzw. Feuchthaltung dieser in Kontakt gebrachten Haut oder Schleimhaut ausreichenden Zeitraums.

2. Das Verfahren nach Anspruch 1, worin die genannten Teilch n aus bioadhesiv m Polym r in ihrer Größe so klassiert sind, daß si in trockenem Zustand durch ein 400 m sh Sieb der US-Standard-

Siebserie hindurchgehen.

3. Das Verfahren nach Anspruch 2, worin die genannten Teilchen aus bioadhesivem Polymer eine zahlengemittelte längste Dimension von 2 bis 5 Mikron aufweisen.

4. Das Verfahren nach einem beliebigen vorhergehenden Anspruch, worin die genannten Teilchen aus bioadhesivem Polymer vor dem in-Kontakt-Bringen in einem physiologisch verträglichen Verdünnungsmittel dispergiert werden.

5. Das Verfahren nach Anspruch 4, worin das genannte physiologisch verträgliche Verdünnungsmittel ein flüssiges Medium ist.

6. Das Verfahren nach Anspruch 5, worin das genannte flüssige Medium Wasser enthält.

7. Das Verfahren nach einem beliebigen vorhergehenden Anspruch, worin die Zusammensetzung umfaßt: 0,25 bis 5 Gewichtsprozent des genannten bioadhesiven Polymers, das (a) eine Vielzahl sich wiederholender Einheiten, von denen mindestens 90 Prozent mindestens eine Carboxyl-Funktion enthalten, und (b) 0,1 bis 1,0 Prozent des genannten Vernetzungsmittels enthält.

8. Das Verfahren nach Anspruch 7, worin die genannte Zusammensetzung gelartige Konsistenz aufweist.

9. Das Verfahren nach Anspruch 8, worin die genannte Zusammensetzung in einer Menge aufgebracht wird, die ausreicht, um 10 bis 50 mg/cm^2 auf der Haut vorzusehen.

10. Das Verfahren nach Anspruch 8, worin die Vaginalschleimhaut mit 1 bis 5 Gramm der genannten Zusammensetzung, die 0,25 bis 3 Gewichtsprozent des genannten bioadhesiven Polymers enthält, in Kontakt gebracht wird.

11. Das Verfahren nach Anspruch 7, worin die genannte Zusammensetzung die Konsistenz einer gießbaren Flüssigkeit aufweist.

12. Das Verfahren nach Anspruch 11, worin die genannte Zusammensetzung in einer Menge aufgebracht wird, die ausreicht, um 0,025 bis 1 mg/cm^2 auf der Schleimhaut des Auges vorzusehen.

13. Das Verfahren nach Anspruch 11, worin die Mundschleimhaut mit 0,25 bis 5 Gewichtsprozent des genannten bioadhesiven Polymers in Kontakt gebracht wird.

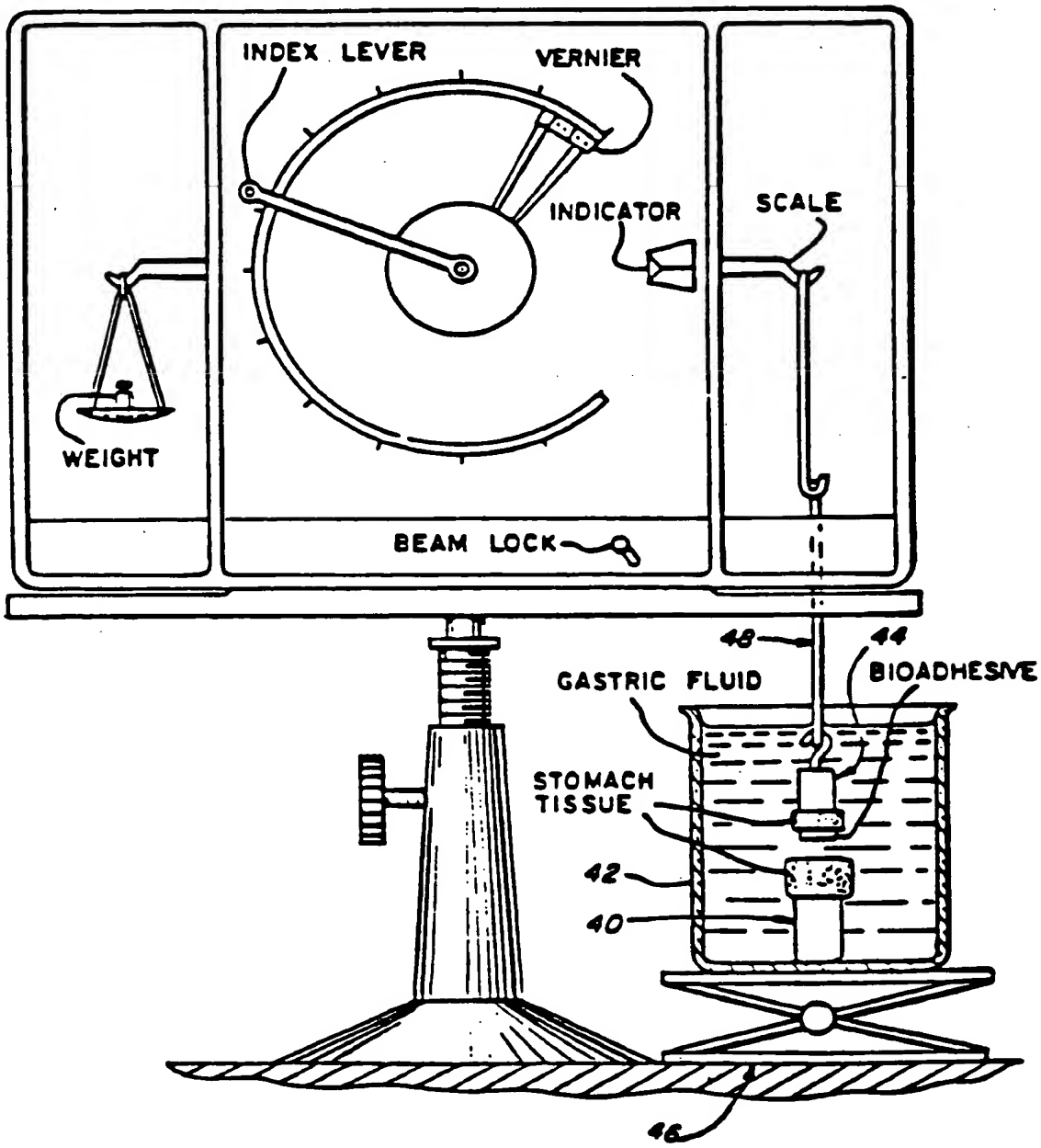
14. Die Verwendung einer bioadhesiven Zusammensetzung als kosmetisches Anfeuchtungs- bzw. Feuchthaltemittel für die Haut oder Schleimhaut von Säugetieren, wobei diese Zusammensetzung im wesentlichen besteht aus Wasser und einer anfeuchtenden bzw. feuchthaltenden Menge eines wasserquellbaren, jedoch wasserunlöslichen, teilchenförmigen, faserigen, vernetzten, Carboxy-funktionellen Polymers, das enthält: (a) eine Vielzahl sich wiederholender Einheiten, von denen mindestens 80 Prozent mindestens eine Carboxyl-Funktion enthalten, und (b) ein im wesentlichen von Polyalkylen-Polyether freies Vernetzungsmittel in einer Menge von 0,05 bis 1,5 Prozent (basierend auf dem Gewicht der unpolymersierten, sich wiederholenden Einheiten und des Vernetzungsmittels).

15. Die Verwendung eines bioadhesiven Polymers in der Herstellung einer Zusammensetzung für die therapeutische Behandlung von Trockenzuständen der Haut oder Schleimhaut von Säugetieren, wobei diese Zusammensetzung im wesentlichen besteht aus Wasser und einer anfeuchtenden bzw. feuchthaltenden Menge eines wasserquellbaren, jedoch wasserunlöslichen, teilcherförmigen, faserigen, vernetzten, Carboxy-funktionellen Polymers, das enthält: (a) eine Vielzahl sich wiederholender Einheiten, von denen mindestesn 80 Prozent mindestens eine Carboxyl-Funktion enthalten, und (b) ein im wesentlichen von Polyalkylen-Polyether freies Vernetzungsmittel in einer Menge von 0,05 bis 1,5 Prozent (basierend auf dem Gewicht der unpolymerisierten, sich wiederholenden Einheiten und des Vernetzungsmittels).

16. Die Verwendung nach Anspruch 15, worin die genannte Zusammensetzung so ist, wie sie in einem der Ansprüche 2 bis 8 definiert ist.

FIG. 1

MODIFIED SURFACE TENSIOMETER



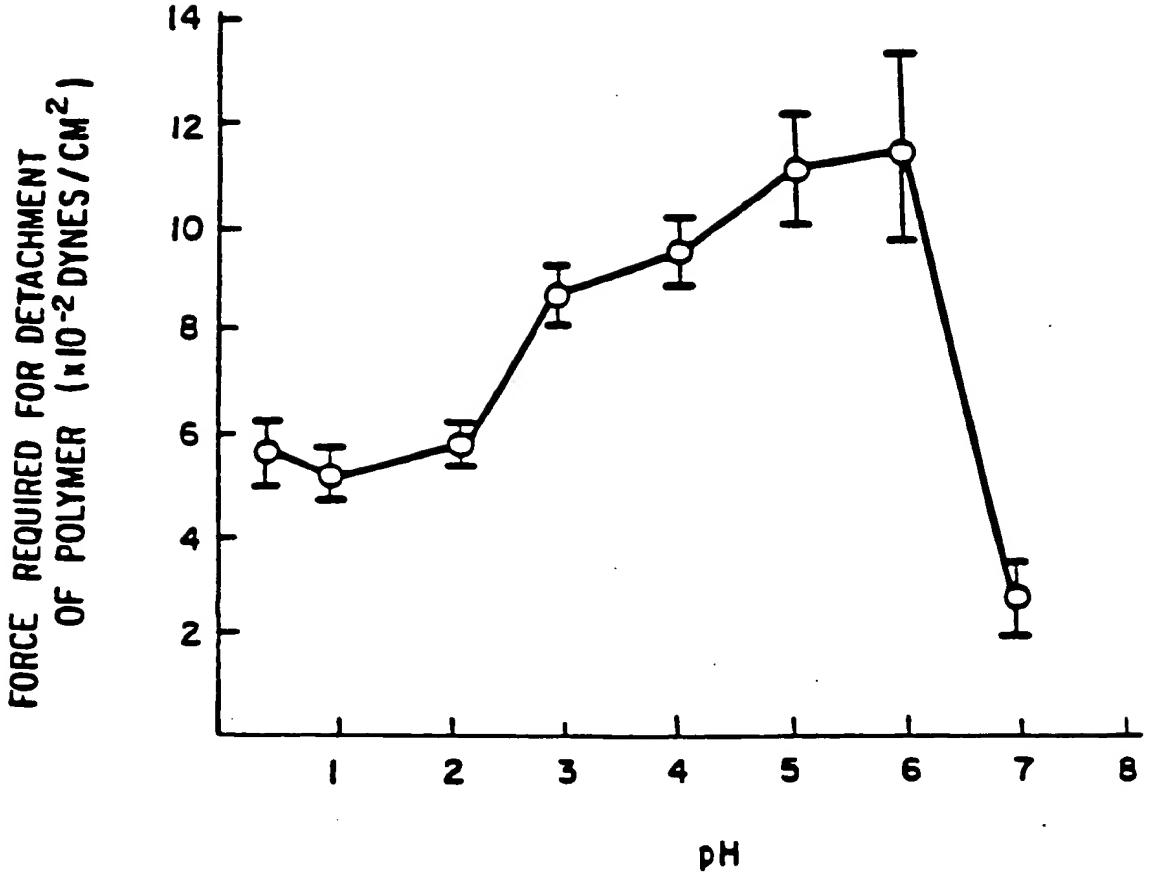

FORCE REQUIRED FOR DETACHMENT OF POLYMER (x10⁻² DYNES/CM²)
14
12
10
8
6
4
2
1
2
3
4
5
6
7
8
pH

FIG. 2